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# (54) Sustained release device

(57) A device e.g. for sub-cutaneous implantation comprises a chamber containing an active ingredient which is released through a capillary bore, the rate of release being governed by the length and diameter of the bore. The active material can be i.a. a pharmaceutical, fungicide or nematocide. The device may be constructed from a cylindrical tube, one or both ends of which are closed with a piece of plastic capillary tube. Exemplified active ingredients are melatonin, insulin, oestradiol, pepsin and salbutanol.

GB 2 243 777 A

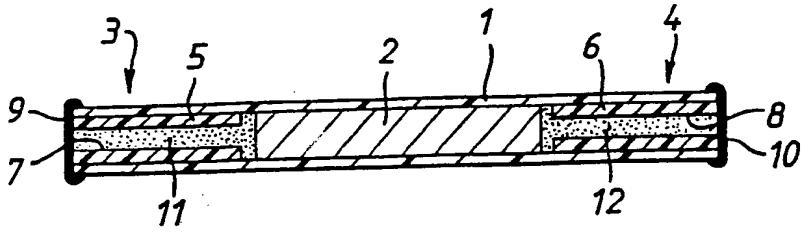
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Fig. 1

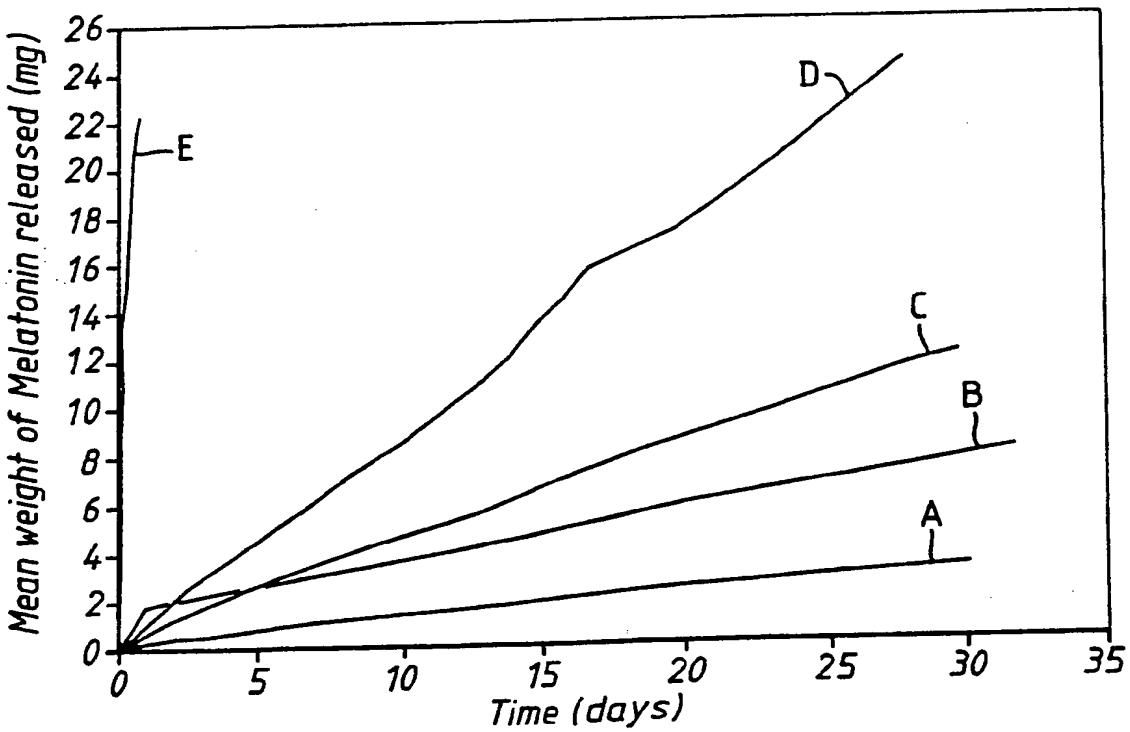
Mean weight of Melatonin released (mg)
26
24
22
20
18
16
14
12
10
8
6
4
2
0
0
5
10
15
20
25
30
35
Time (days)
D
E
C
B
A

Fig. 2

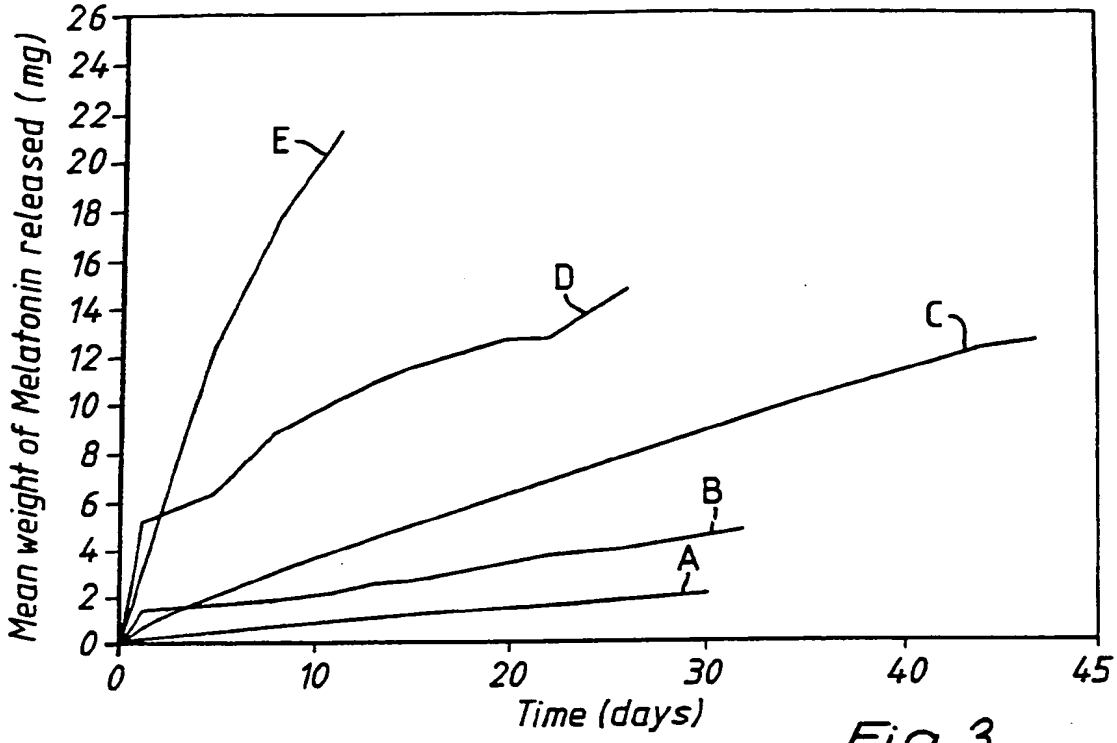


Fig. 3

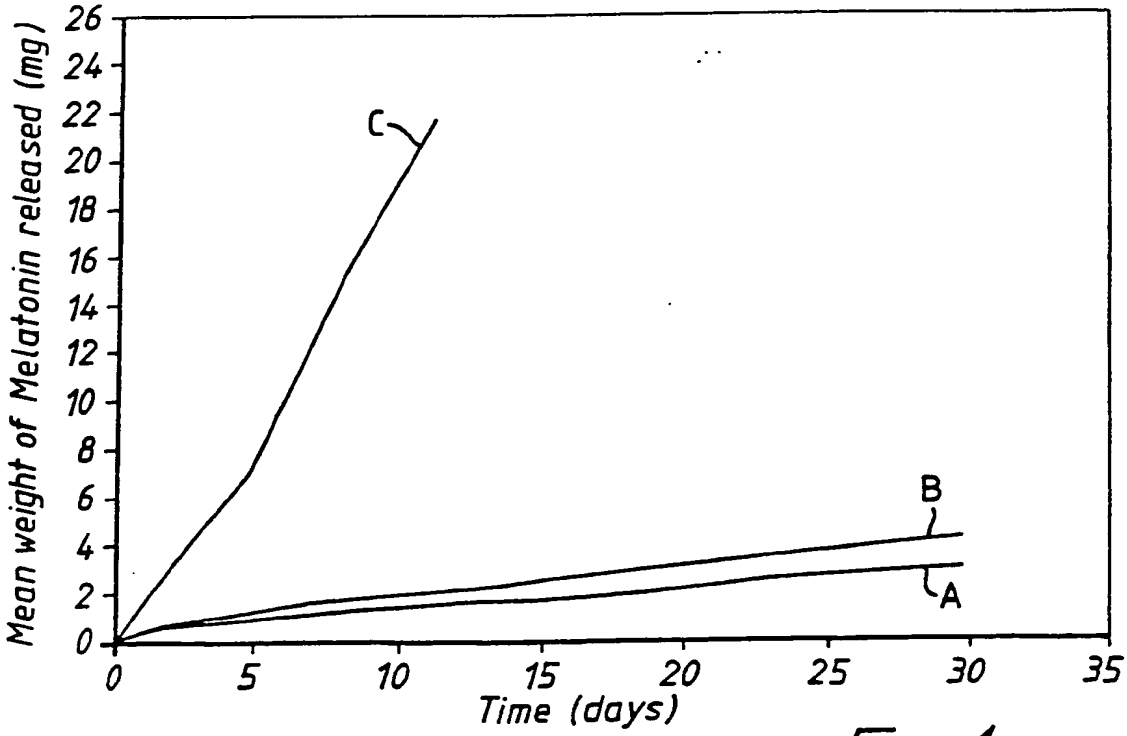


Fig. 4

3NSDOCID: <GB 2243777A I >

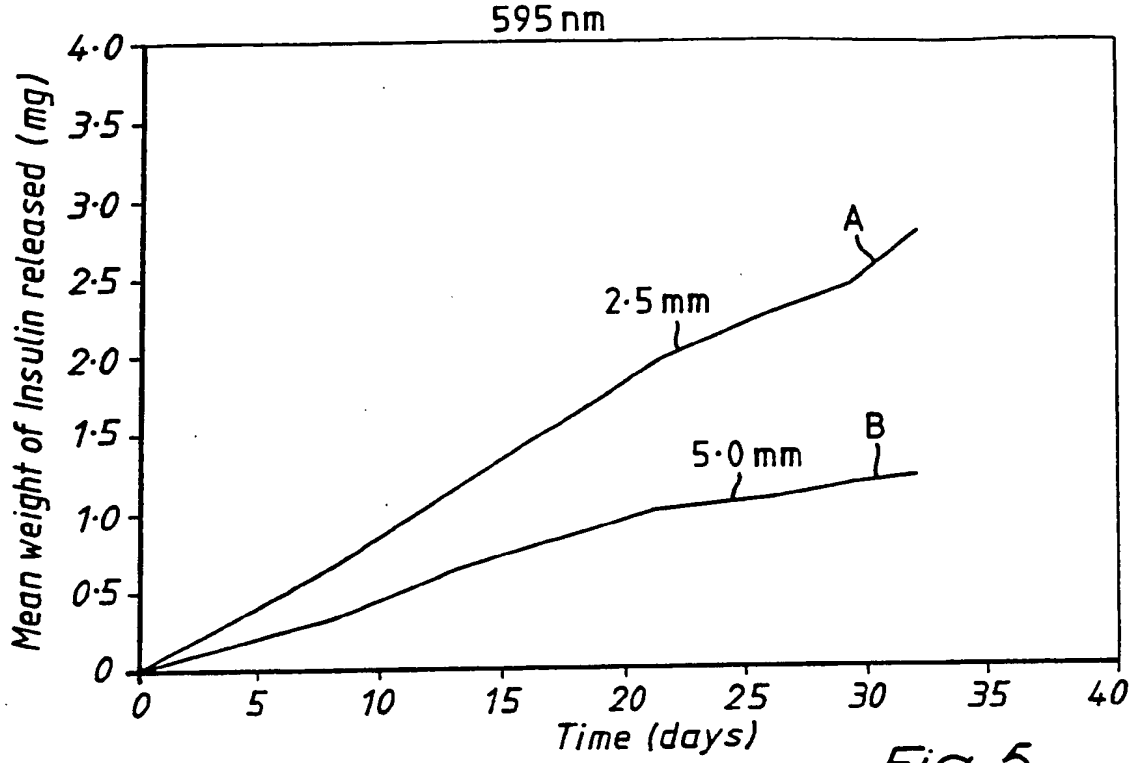
595 nm
Mean weight of Insulin released (mg)
4·0
3·5
3·0
2·5
2·0
1·5
1·0
0·5
0
A
2·5 mm
B
5·0 mm
0
5
10
15
20
25
30
35
40
Time (days)

Fig. 5

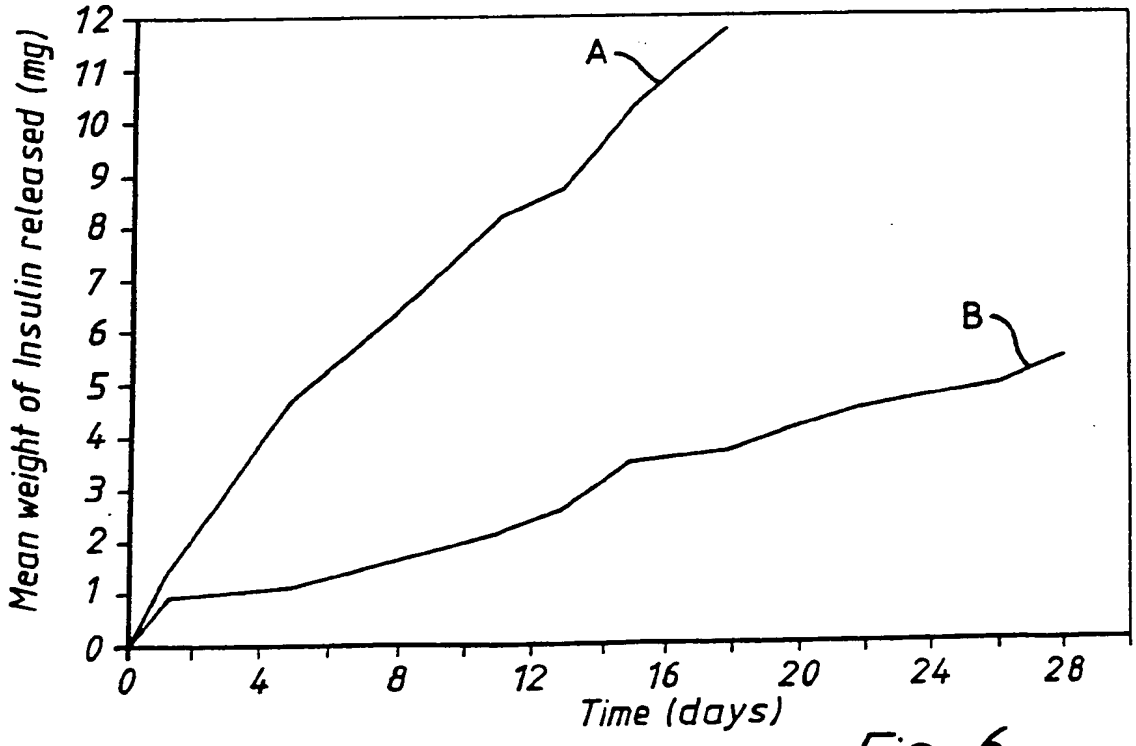
Mean weight of Insulin released (mg)
12
11
10
9
8
7
6
5
4
3
2
1
0
A
B
0
4
8
12
16
20
24
28
Time (days)

Fig. 6

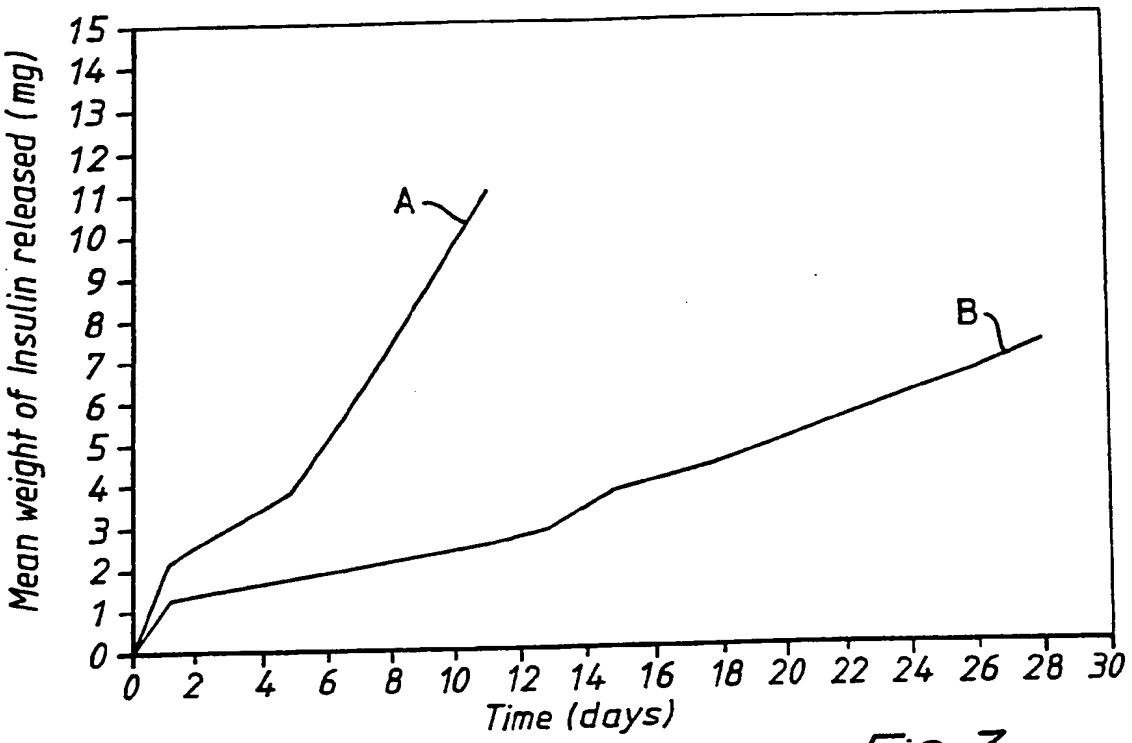


Fig. 7

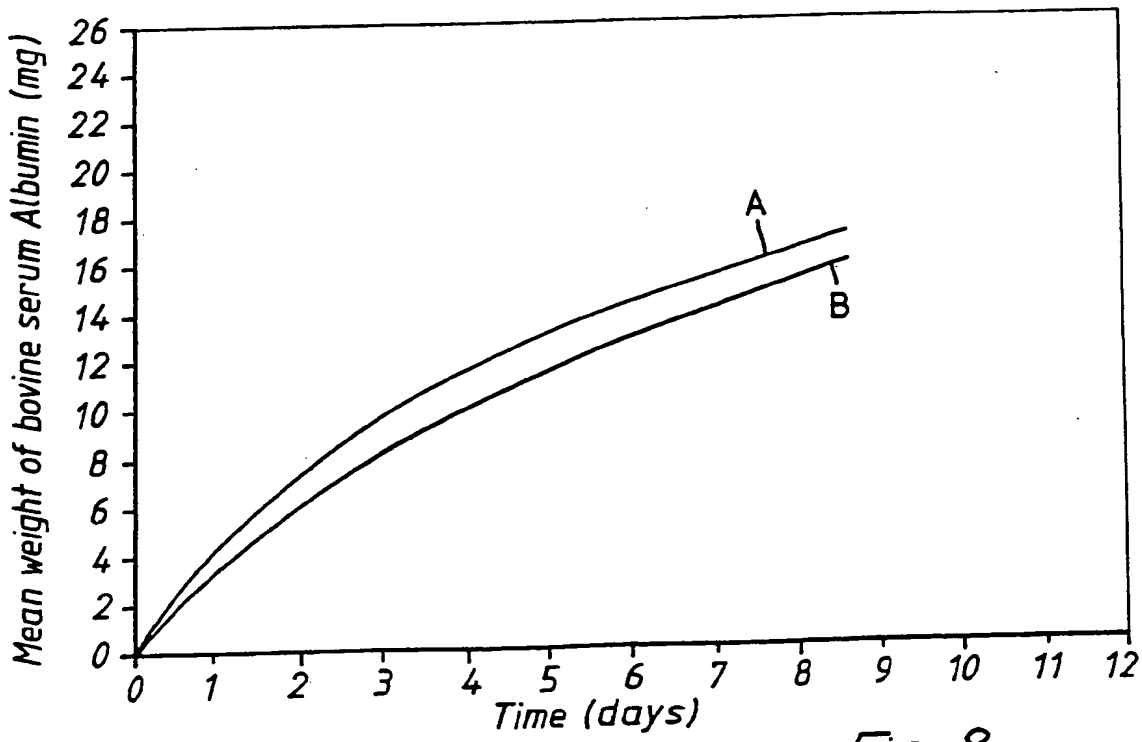


Fig. 8

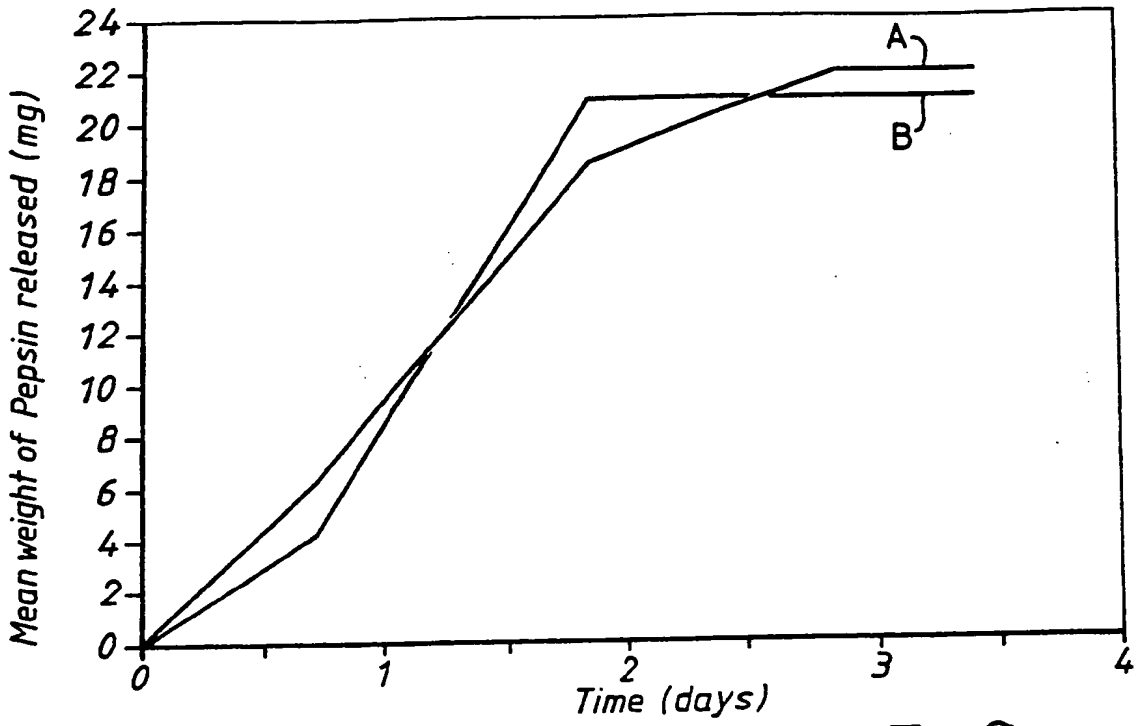
Mean weight of Pepsin released (mg)
24
22
20
18
16
14
12
10
8
6
4
2
0
0
1
2
3
4
Time (days)
A
B

Fig. 9

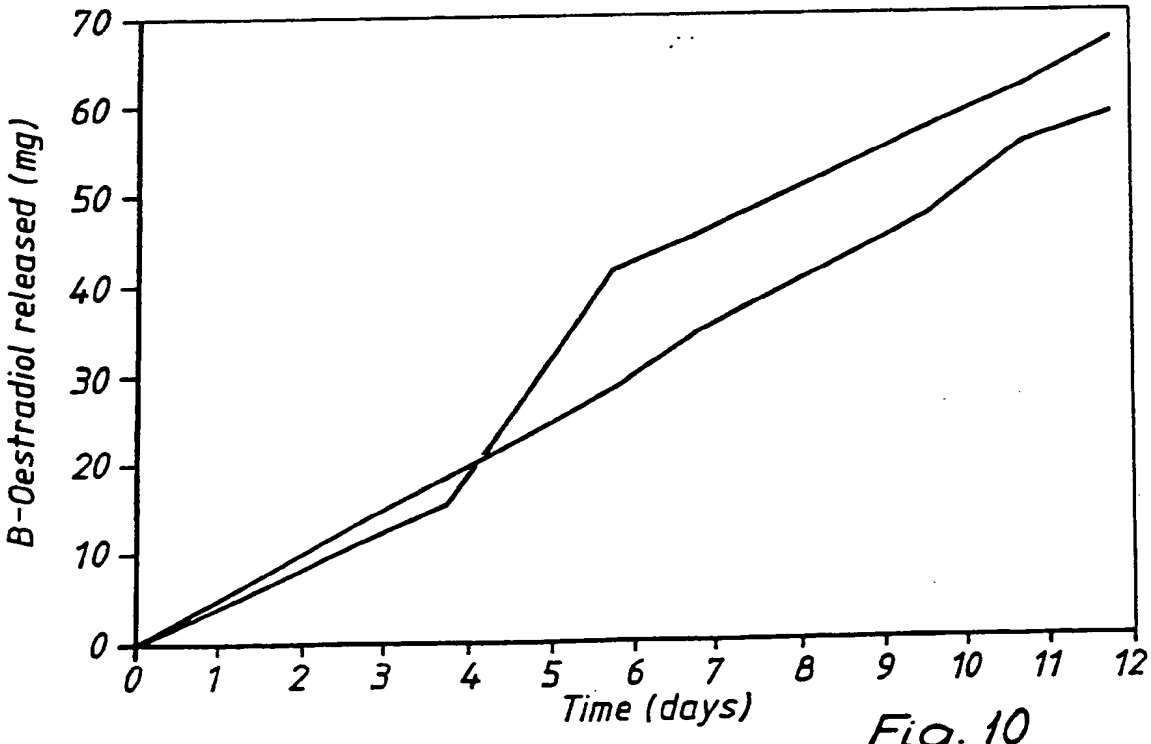
B-Oestradiol released (mg)
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
11
12
Time (days)

Fig. 10

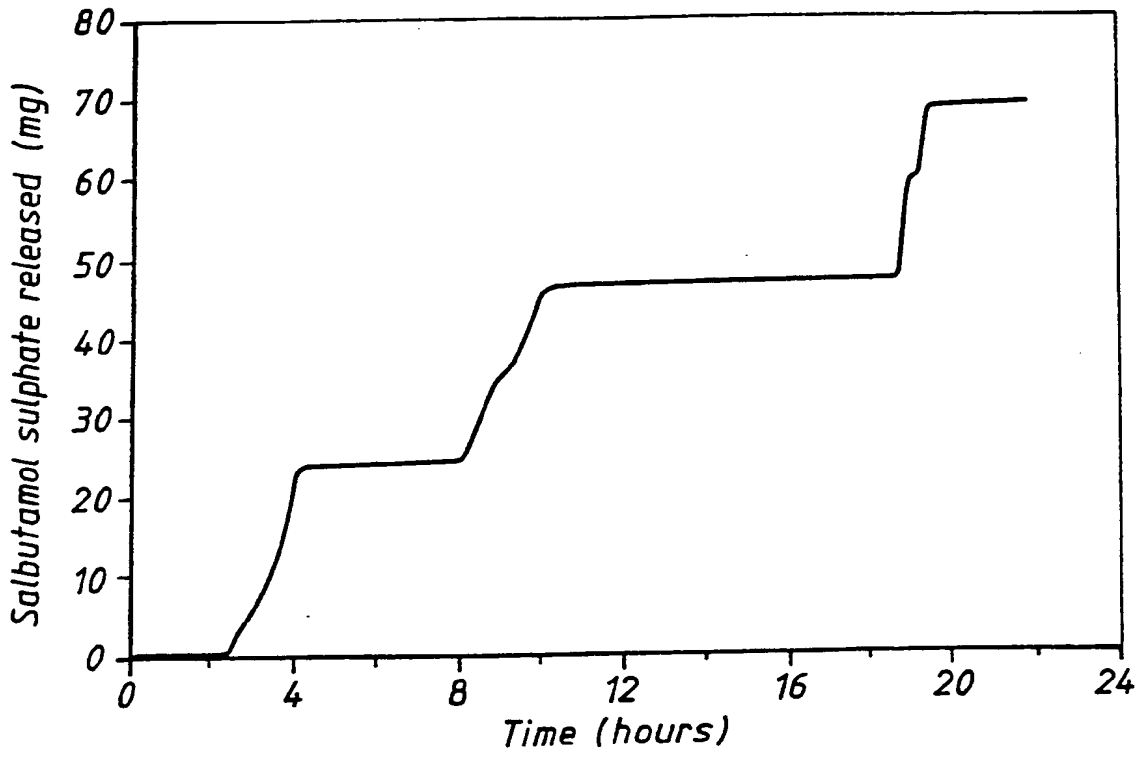


Fig. 11

# SUSTAINED RELEASE DEVICE

The present invention relates to sustained release devices which allow for the sustained release of an active ingredient when the device is in contact with body fluids.

There is a need in the medical field for ways of administering an active ingredient to a patient over a prolonged period of time so that the patient receives a continuous dose. This is particularly true where the active ingredient is rapidly cleared from the body by the body's own processes, so that administration of the active ingredient at inconveniently frequent intervals is required. The literature is full of proposals for such sustained release devices, both for humans and animals. However, many of these are of quite complex construction.

It is a particular object of the present invention to provide a sustained release device which is small enough to allow for sub-cutaneous implantation (although other uses may be possible). U.S. patents 3946734, 3924622 and 3851648 disclose sustained release devices. U.S. 3946734 discloses apparatus wherein the rate of release of the drug is controlled by means of a neutral hydrophilic material though which the drug diffuses.

It is an object of the present invention to provide a sustained release device of simple construction which is capable of mass production at an economic cost.

The present invention provides a sustained release device for the sustained release of an active ingredient

when the device is in contact with body fluids, which comprises

a chamber containing the active ingredient and having an outlet therefrom; and

a capillary bore extending from the outlet for controlling the rate of release of the active ingredient from the chamber into the body fluid; the length and diameter of the bore being selected to be the controlling factor determining the release rate of the active ingredient.

Generally, the active ingredients will be present in the form of a solid tablet, granules or particles, or in the form of a paste, gel or as viscous fluid or other formulation. After the device has been introduced into the body, body fluid enters the device through the capillary bore and establishes a substantially saturated solution of the active ingredient within the chamber. The rate of release of active ingredient from the device is then controlled predominantly by the length and diameter of the capillary bore, rather than by the rate of dissolution of the active ingredient or any other factor. In this way, the device may provide a substantially constant rate of release of active ingredient over the useful lifetime of the device.

In one configuration the chamber may be in the form of a length of cylindrical tube containing the active ingredient and having a length of capillary tubing

inserted into at least one of the ends of the tube. The device will generally have a length of 5 -100 mm (preferably 10 - 40 mm) and an external diameter of 1 -40 mm (preferably 1-5mm). The device can be formed of a plastics material, a ceramic material, a metal such as stainless steel, or glass. It is particularly preferred to form the device from a biodegradable or bioresorbable polymer so that once the device is exhausted, it is gradually broken down and eliminated from the body, so that there is no need to remove the used device. This is particularly valuable in the case of humans. Suitable non-degradable polymers include polyethylene, polyvinylchloride, polypropylene, polytetrafluorethylene, polysilicones such as silicone rubber, polymethylmethacrylate, polyamide, polycarbonates, polystyrene, polyformaldehydes, polyesters, cellulose acetates, and nitrocellulose. Suitable biodegradable polymers include polylactides, polyglycolides, poly(lactide-co-glycolide),polydioxanone and poly (hydroxybutyric acid). Suitable ceramic materials include aluminium oxides, and silicon nitrides. Suitable metals include stainless steel, titanium or its alloys, and aluminium and alloys thereof.

In alternative constructions, the chamber and capillary tubing may be integrally produced by injection moulding, casting or die stamping the device in two or more portions e.g. a male and a female portion. The

chamber is then filled prior to union of the various portions and their sealing together by gluing, fusing, welding, or tightness of fit.

The rate of release of the active ingredient is determined substantially by the length and diameter of the capillary bore. Generally, the capillary bore is from 1 - 30 mm, preferably 2-15mm long and of a diameter 0.1 to 10mm, preferably 0.2-2 mm, depending on the characteristics of the active ingredient, such as its molecular weight, molecular size, its solubility, and the viscosity of its solution in the body fluid. The capillary bore may be straight or curved or even spiral shaped . Moreover, the term "diameter" is used loosely to indicate the internal width of the capillary bore, whether that be round, square, oval etc. in cross sectional configuration.

The sustained release device may have one outlet or a plurality of outlets each provided with its own capillary bore. In fact, the chamber may be compartmentalised, each compartment being provided with its own active ingredient and its release profile being controlled by its own capillary tube. The compartments may contain the same active ingredient if a complex release profile is to be built up, or may be provided with different active ingredients which may be administered at the same or different rates, wher a number of active ingr dients are to be administered to the patient. When the device is

charged with the active ingredient in lamellar form with a layer of an inert soluble material between adjacent active layers then a complex profile can be provided, affording a sustained delivery of the active(s) with intermittent delays.

The sustained release device is primarily intended for subcutaneous implantation, insertion into body cavities and may also be used for oral administration and release of active ingredient in the stomach or intestines, and for rectal, vaginal or intrauterine use. In the case of ruminant animals, the device may be administered as an intraruminal bolus having suitable weighted or geometric means for retaining the device in the animal's stomach. The term "body fluid" is to be interpreted accordingly.

If required, the open end of the capillary tube may be provided with a copy which dissolves away on administration, for example formed from a sugar or gelatin. Similarly the bore may be filled with a soluble material thereby improving the integrity of the device, but which material dissolves away on administration facilitating the ingress of body fluids into the capillary tubing. Additionally this soluble material may contain active ingredient to provide an initial surge of active ingredient to the patient.

The invention is of broad applicability to the dispensing of biologically active materials. Examples of classes of active materials include pharmaceuticals, bacteriostats, viruscides, insecticides, herbicides, larvicides, fungicides, algaecides, nematocides, antifoulants for marine growth prevention, enzymes and preservatives.

The active ingredient may be a medicament, a contraceptive, or for prophylatic, diagnostic or nutritional use.

Specific classes of drug which may be utilised as the active material in the device of this invention include hypnotics, sedatives, tranquilisers, anti-pyretics, anti-inflammatory agents, anti-histamines, anti-tussives, anti-convulsants, anti-asthmatics, muscle relaxants, anti-tumour agents, for example those for the treatment of malignant neoplasia, local anaesthetics, anti-Parkinson agents, diuretics, for example those containing potassium, such as potassium chloride, preparations for the treatment of mental illness, for example preparations containing lithium for use in the treatment of manic depression or containing prostaglandins for the treatment of schizophrenia, anti-spasmodics, anti-ulcer agents, beta blockers such as atenolol and metoprolol; calcium antagonists such as nifedipine and nitrendipine, ACE inhibitors such as enalapril and captopril,beta agonists such as salbutamol and terbutaline, preparations containing various substances for the treatment of infection by pathogens including anti-fungal agents, for example metronidazole, anti-parasitic agents and other anti-microbials, anti-malarials, cardiovascular agents, preparations containing hormones, for example androgenic, estrogenic and progestational hormones, notably steroids such as oestradiol, sympathomimetic agents, hypoglycaemic agents, contraceptives, nutritional agents,vitamins, peptides and prot ins, nitrates such as isorbide dinitrate, mononitrate and GTN; xanthines such as

theophylline; NSAID'S such as piroxicam and diclofenac; alpha blockers such as prazosine and alfuzosine; antivirals such as acyclovir, zidovudine and ampligen, cephalosporins such as cefaclor, antispasmodics such as alverine and salicylates such as 5 amino salicylic acid; preparations containing enzymes of various types of activity, for example chymotrypsin, preparations containing analgesics, for example aspirin,or fentanyl and agents with many other types of action including nematocides and other agents of veterinary application. Mixtures of active substances may be incorporated into the sustained release device.

The sustained release devices of this invention are also useful in the treatment of drug dependency, and for diabetes and pernicious anaemia where, for example, the controlled release of insulin and cobalamin, respectively, may be utilised.

Moreover, the release devices of this invention are suited to treatment, both prophylactic and therapeutic, of tropical diseases; for example malaria, leprosy, schistosomiasis and clonorchiasis. Examples of drugs which can be used as biologically active substance in release devices of this invention for the treatment of thes and other tropical diseases includ quinin , sulphonamides, rifamycin, clofazimine, thiambutosine, chlorphenyl derivatives, cycloguanil, pyrimethamine, sulphadiazine, trimethoprim, quinoline derivativ s such

as pamaquin, chloroquine, pentaquine, primaquine and amodiaquine,pararosaniline, sulphamethizole, quinacrine, dapsone, sodium sulphoxone, sulphetrone, and sodium chaulmoograte. Drugs of particular effectiveness are cycloguanil, pyrimethamine and sulphadiazine.

The release devices of this invention are also very well suited to veterinary applications. Examples include preparations of antibiotics for general antibacterial activity and also in the treatment of anaplasmosis in cattle; preparations for provision of a wide spectrum of activity against both ectoparasites, for example termites and endoparasites including anthropods, arrested larvae stages of nematodes, lungworms and general strongyles: these may comprise avermectins; preparations for provision of activity against tremotode, cestode and roundworm infections: these may comprise amoscanate and praziquantel: preparations for provision of activity against theileria in cattle: these may comprise biologically active naphthoquinones such as menoctone; preparations for provision of activity against babesiosis in cattle, horses and dogs: these may comprise berenil, amidocarb and diampron; preparations for provision of activity against liver fluke in sheep and cattle and against Haemonchus species: these may comprise closantel.

Embodiments of the present invention will now be described by way of example only with ref rence to the accompanying drawings and the following exampl s, wherein

Figure 1 is an enlarged cross-sectional view of a sustained release device having capillary tubing-controlled openings at either end intended for implantation.

Figures 2,3 and 4 show release profiles for the rate of release of melatonin from devices having varying pore lengths placed in water;

Figures 5,6 and 7 show release profiles for insulin into 0.001M HCl at various pore diameters;

Figure 8 shows release profiles for bovine serum albumin into water;

Figure 9 shows a release profile for pepsin into water;

Figure 10 shows a release profile for B-oestradiol into water; and

Figure 11 shows the results of a pulse release device.

Figure 1 shows a sustained release device comprising a length of outer tubing 1 formed of a plastics material and containing a drug matrix 2. Each end 3,4 of the tube has inserted therein a respective length of plastics capillary tubing 5,6 sealed to the outer tubing by means of a tight fit. Each capillary tube has a respective central bore 7,8 whose length and internal diameter control the rate of release of the drug. The device is suitable for subcutaneous implantation. Each end is sealed with a water soluble sugar end cap 9,10 with th capillary tube bones 7,8 filled with water soluble material at 11 and 12 respectively. Since entrapped air can block the bores,

care was taken to ensure that air was excluded.

Assembly of Devices

Polypropylene and polyethylene tubing (ex Portex) were used as both the pores and outer sleeves or tubing in the device. It was ensured that the inner diameter of the exterior sleeve was slightly smaller or equal to the outer diameter of the pore to provide a tight fit between the pore and exterior sleeve.

After carefully selecting the tubings appropriate lengths for the exterior sleeves and pores were cut to the required lengths by a scalpel. Pores of 2.5, 5 and 10mm were subsequently selected by measuring their lengths with a Vernier Caliper (ex Mitutoyo) with an accuracy of ±0.08mm.

One end of the exterior sleeve was blocked by introducing a drill blank up to the length required for the pore and through the other open end, the required quantity of the drug was introduced and compacted with another drill blank. A pore was introduced in this open end. Subsequently the drill blank from the other end of the exterior sleeve was replaced with the other pore such that the inner edges of the pores are touching the compacted drug.

Since any entrapped air can block the openings of the pores, appropriate measures were taken to exclud the air. Prior to th release studies, this was achi ved either by injecting a small volume of water through pores

or by sonicating, for a minute or two, the devices which were immersed in a beaker of water. Subsequently once the release study was initiated the devices were carefully observed for initial few days and bubbles if formed at the openings of the pores were removed simply by tapping the bottles in which the release studies were carried out.

IN-VITRO RELEASE RATE TESTING

This was carried out either in degassed double distilled water (pH 5.5) or 0.001M HCl (pH 3.0) as indicated, contained in glass bottles which were placed in a thermostatted (at 37°C) water bath shaking at 30 strokes/minute. Spectrophotometric determinations were carried out at the appropriate wavelength on aliquots which were manually removed from the dissolution vessels and subsequently replaced after analysis.

Once the absorbance of a given release medium reached a value of 1.2 au, it was replaced with an appropriate volume of fresh medium. This was appropriately accounted for in the quantitation of the total amount released.

Example 1 (melatonin)

A sustained release device similar to that shown in Figure 1 was used to investigate the release rate of melatonin into water at 37°C, according to the regime described above.

The mean dissolution profiles of a number of trials are given in Figures 2-4 for pore lengths of 2.5mm (Figure 2), 5.0mm (Figure 3) and 10.0mm (Figure 4) respectively. In Figure 2 the particulars of the devices tested were:

| Profiles | Pore i.d. (mm) | Number of Devices |
|---|---|---|
| A | 0.86 | 9 |
| B | 1.19 | 2 |
| C | 1.40 | 2 |
| D | 1.50 | 5 |
| E | 2.0 | 1 |

In Figure 3 the particulars of the devices tested were:

| Profiles | Pore i.d. (mm) | Number of Devices |
|---|---|---|
| A | 0.86 | 7 |
| B | 1.19 | 3 |
| C | 1.40 | 6 |
| D | 1.50 | 3 |
| E | 2.0 | 1 |

In Figure 4 the particulars of the devices tested were:

| Profiles | Pore i.d. (mm) | Number of Devices |
|---|---|---|
| A | 1.19 | 2 |
| B | 1.40 | 3 |
| C | 2.0 | 3 |

Example 2 (Insulin)

The procedure described in Example 1 was repeated with insulin.

The dissolution studies were carried out in an acidic medium (pH3) and the aliquots at different time intervals were assayed by two different methods which measure absorbance at 212nm and 595nm. The method which assayed at 595nm utilised the Pierce Protein Assay Reagent. This is based on the absorbance shift from 465 to 595nm which occurs when Coomassie Blue G-250 binds to proteins in an acidic solution. For protein concentrations over a wide range, the colour response is relatively linear and thus permits the protein determinations, whereas in the other method the release aliquots were directly measured for their absorbance at 212nm.

Figures 5 to 7 give the mean dissolution profiles of a number of trials at internal pore diameters of 0.38mm (Figure 5), 0.86mm (Figure 6) and 1.19mm (Figure 7). In Figures 5, 6 and 7 Profile A represents the results of devices having a pore length of 2.5mm and Profile B those of devices having a pore length of 5mm.

Example 3 (Bovine Serum Albumin)

The procedure described in Example 1 was repeated with bovine serum albumin (BSA) of molecular weight approximately 77,000 in order to demonstrate utility with active ingredients of high molecular weight. Figure 8 shows the mean dissolution profile of

a number of tests at a pore size of 0.86mm. Profile A represents the results of devices having a pore length of 3.0mm and Profile B that of devices having a pore length of 5.0mm.

Example 4 (Pepsin)

The procedure was repeated using pepsin as the active agent using devices having an internal pore diameter of 0.86mm. The mean dissolution profiles are given in Figure 9. Profile A represents the results from devices having a pore length of 3.0mm and Profile B those from devices having a pore length of 5.0mm.

Example 5 (B-Oestradiol)

The procedure described in Example 1 was repeated with B-oestradiol which is an example of a potent steroid with low solubility in water. An HPLC assay method was used to monitor its release characteristics from a device having a total length of 10mm, a pore length of 2.5mm, a pore inner diameter of 2.0mm, an exterior tube having an external diameter of 3.88mm and an internal diameter of 3.0mm and a pore tube of external diameter 3.0mm and internal diameter 2.0mm.

Since B-Oestradiol is a low solubility drug, prior to the release study its saturated solubility in water at 37°C (~28ug $ml^{-1}$), was determined by the HPLC method. In the release experiments it was ensured that the concentration of the release medium did not exceed the 20% of the saturated value. Hence when the concentration reached this level the release medium was changed and this was appropriately accounted for in the accumulative release.

Example 6 (pulse release of salbutamol sulphate)

Using polyethylene tubing (see Table 1 for details) one device was assembled such that its one end was closed by a solid rubber plug. Through the open end multilayers of drug and inert tablet were built. Firstly the device was charged with 25mg of Salbutamol sulphate which was compacted and an inert tablet was placed on top of the Salbutamol sulphate. This layer of drug followed by

tablet was repeated two more times such that a gap of 5mm remained above the top tablet (see Figure 1) for the Pore tube. The Pore tube was made to fit in the exterior tubing by the use of appropriate collar tubing.

The inert tablet was prepared by mixing the following in a turbula mixer. The mixture was tabletted on a Manesty F3 Tabletting machine.

| | |
|---|---|
| Lactose | 70% |
| PEG 8000 | 29% |
| Mg.Stearate | 1% |

Tablet Weight - 98.5mg

Tablet Diameter - 6.5mm

Table 1

| | Inside Diameter | Outside Diameter | Length |
|---|---|---|---|
| Outer Tubing | 6.50 | 9.60 | 25.60 |
| Pore Tubing | 1.90 | 3.18 | 5.0 |
| Collar Tubing | 3.20 | 6.50 | 5.0 |

The Pore of the device was filled with water, to avoid any bubble formation, and immersed into a litre of water at 37°C stirr d at 50rpm. The aliquots were continuously pumped through a peristaltic pump into a flow cell placed in a UV spectrophotometer (Perkin Elmer Lambda 5) and the

concentration of the aliquots were monitored at 226nm automatically. The results were quantified and plotted as amount of Salbutamol sulphate released vs time (hours) (see Figure 11)

RESULTS

The inner tablet dissolved slowly until completely disappeared, indicated by the lag time in the profile (Figure 2), exposing the drug to the medium which appeared on a pulse indicated by a step in the profile and so on. The lag time prolonged going from Tablet 1 to 3 outer to inner because the path length within the device was increasing progressively with the disappearance of upper tablet(s).

CLAIMS

1. A sustained release device for the sustained release of an active ingredient when the device is in contact with fluids, which comprises:

a chamber containing the active ingredient and having an outlet therefrom; and

a capillary bore extending from the outlet for controlling the rate of release of the active ingredient from the chamber into the fluid;

the length and diameter of the bore being selected to be the controlling factor determining the release rate of the active ingredient.

2. A device as claimed in claim 1, in which the chamber is in the form of a hollow cylindrical tube and having a length of capillary tubing inserted into at least one end portion thereof.

3. A device as claimed in claim 1 wherein at least a portion of the chamber is formed integrally with the capillary tubing, initially separate portions of the chamber being secured together to form said chamber.

4. A device according to any of the preceding claims wherein the capillary bore has a diameter of from 0.1 to 10.0mm.

5. A device according to any of the preceding claims wherein the capillary bore is from 1.0 to 30.0mm long.

6. A device according to any of the preceding claims wherein outer end portions of the capillary bore are sealed by a water soluble compound.

7. A device as claimed in any of the preceding claims wherein there are provided a plurality of outlets from the chamber, each outlet being associated with a bore.

8. A device as claimed in any one of the preceding claims wherein the capillary bore is non-rectilinear.

9. A device as claimed in any of the preceding claims wherein the bore is filled with a soluble material, adapted to dissolve in use so as to facilitate ingress of fluid.

10. A device as claimed in any of the preceding claims wherein the chamber is adapated to contain active ingredients in the form of solid tablets, granules or particles, paste, gel or viscous fluid.

11. A device according to claim 1 substantially as hereinbefore described with reference to the accompanying drawings.

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